Remarks

Claims 1-4, 33, 34, 44-47, 51, 52, and 55-62 pending in the subject application and currently stand rejected. Favorable reconsideration of the pending claims is respectfully requested in view of the following remarks.

All pending claims stand rejected under 35 USC §103(a) as obvious over the combined disclosures of Uchegbu *et al* and Wang *et al* Applicants respectfully traverse and assert that the combination of references does not render the claims even *prima facie* obvious.

Uchegbu *et al*. relates to a quaternary ammonium palmitoyl glycol chitosan (GCPQ) polysoap with a M_w of 178,000 g mol^{-1}. Uchegbu *et al* teaches that this high molecular weight is critical to ensuring that the polysoap is non-haemolytic and non-cytotoxic. Uchegbu *et al* in section 3.6, page 192, states that "the high molecular weight of the polymers prevents the effective partitioning into and hence solubilization of the erythrocyte membranes." (Emphasis added). Furthermore, Uchegbu *et al* at page 197, col. 2, concludes:

> The high molecular weight of the polymer is believed to be responsible for the lack of haemolytic activity and significant cytotoxicity of GCPQ and although polysoaps are known to interact with membranes (Yang *et al*., 1998), the non-destruction of the erythrocytes is an advantage for biomedical applications. (Emphasis added).

One of ordinary skill in the art would clearly appreciate from Uchegbu *et al*. that a high molecular weight, far exceeding the claimed M_w range of the instant invention, would be required to avoid the very negative *in vivo* and *in vitro* effects of heamolysis and cytotoxicity. Uchegbu *et al* therefore clearly and strongly teaches away from, and offers no motivation to combine with, any reference teaching a relatively low M_w range such as from about 2kDa-30kDa, as in the instantly claimed subject matter. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Based on Uchegbu *et al*'s teachings that high molecular weight of the polymer is desirable, the skilled artisan would not look to Wang *et al* for any suggested modifications. For the sake of argument, even if one did look to Wang *et al*, Wang *et al* make no mention of the solubilization properties of the chitosan polymers. Thus there would be no motivation to look to Wang when faced with the problem of solubilizing hydrophobic drugs. Indeed the only thing that can be learnt by

combining Wang *et al* with Uchegbu *et al* is the fact that the molecular weight of chitosan amphiphiles controls the particle size of chitosan amphiphile self assemblies. There is no teaching regarding how this would affect the solubilization of a hydrophobic drug; and there is no teaching regarding the claimed range of 2kDa-30kDa, which is critical to the claimed invention.

Furthermore, Uchegbu *et al* teach that a gel forms with chitosan polymers above a concentration of 10 mg mL^{-1}. However when polymers of the present invention are used in the molecular weight range claimed gels are not seen at a concentration of 10 - 40 mg mL^{-1}. This is advantageous in the present invention where a gel would not be suitable for intravenous administration. As support for this, see attached Appendix 1 which demonstrates the viscosity of 13kDa GCPQ (a polymer according to the invention). It can be seen that below 30kDa there is virtually no increase in Dynamic Viscosity.

Although the foregoing remarks have been directed at claim 1, claims 2-4, 33, 34, 44-47, 51, 52, and 55-62 depend directly or indirectly from claim 1. Any claim dependent from a non-obvious claim is also non-obvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir.1988).
For all the foregoing reasons, the §103(a) rejection of claims 1-4, 33, 34, 44-47, 51, 52, and 55-62 should be withdrawn upon reconsideration.

Further proof of the criticality of the claimed molecular weight range of 2kDa-30kDa can be seen in Appendices 2-6, submitted herewith.

Appendix 2, appended hereto, illustrates the effect of quaternary ammonium cetyl glycol chitosan (GCHQ) molecular weight on particle size and prednisolone solubilization. GCHQ is a polymer as required by amended claim 1 of this application and prednisolone is a hydrophobic drug. Appendix 1 shows that above 30kDa the solubilization of prednisolone drops markedly.

Below 2kDa the ability of the polymer to encapsulate hydrophobic drug is very poor. Appendix 3, appended hereto, depicts results of experiments where the ability of a polymer according to this invention to solubilize propofol (a hydrophobic drug) was tested. Figure 1 shows that a relatively high amount of drug is encapsulated when polymer with a Mw of 9.3kDa and a backbone Mn of 4.1kDa is used. When a polymer with a lower molecular weight is used (Mn=1.9kDa) as in Figure 2, the encapsulation drops markedly. The scales on the y axis demonstrate this.

Appendix 4 appended hereto, shows the biological effect of intravenous injection of palmitoyl Leucine-Enkephalin in terms of the pain relief it achieves when formulated with 10kDa polymer (within the scope of the invention) and 1kDa polymer (outside the scope of the invention). Palmitoyl leucine enkephalin is a hydrophobic prodrug of leucine enkephalin. From the data it is clear that particles prepared from polymers of 10kDa produce higher pain relief when used to deliver palmitoyl Leucine-Enkephalin, whereas the pain relief produced when particles are prepared from a 1kDa polymer is of lower intensity.

Further support for non-obviousness of the claimed invention can be found in Appendices 5 and 6. Appendix 5 shows significantly lower levels of drug encapsulation when a polymer outside the molecular weight range claimed is used, when compared to polymers within the molecular weight range. High levels of drug encapsulation ensure that excessive levels of excipient (the polymer in this case) do not have to be used. Excessive levels of excipient may make dosing less feasible.

Appendix 6 shows significantly higher viscosity formulations obtained with polymers outside of the molecular weight range. High viscosity formulations are disadvantageous in this field because, for example, they cannot be injected intravenously.

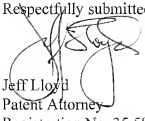
For the foregoing reasons, neither Uchegbu *et al* nor Wang *et al*, alone or in combination, suggests the criticality of the claimed molecular weight range.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the claims as currently pending are in condition for allowance, and such action is respectfully requested.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Respectfully submitted,



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Attachments: Request for Continued Examination
Appendices 1-6

Appendix 1

The viscosity of 13 kDa GCPQ

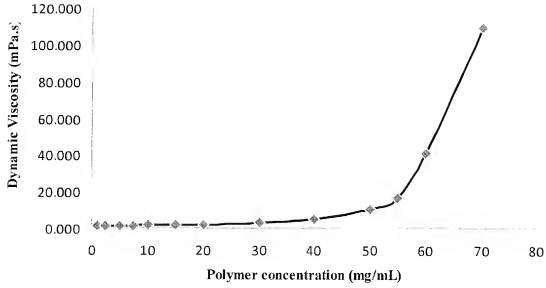

Figure 5: The dynamic viscosity of 13kDa GCPQ, Mw = 12.9kDa at room temperature. Viscosity was determined using a capillary viscometer and no gel formation was observed below 40 mg mL^{-1}. The viscosity of water was measured as 1.002 mPas at room temperature.

Appendix 2

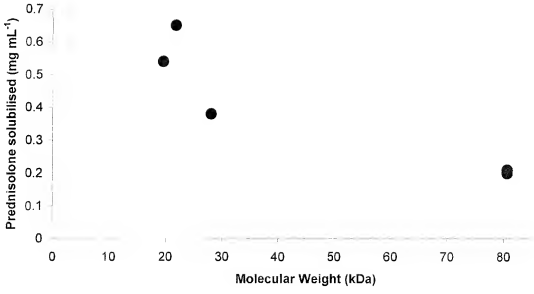

Figure 1: The effect of GCHQ molecular weight on the solubilisation of prednisolone: level of cetyl groups = 2 – 4 mole % (2 – 4 monomers are modified per 100 monomers), level of quaternary ammonium groups = 2 – 5 molc% (2 – 5 monomers are modified per 100 monomers). GCHQ (1 mg mL^{-1}) was probe sonicated with prednisolone (1 mg mL^{-1}), the formulation filtered (0.45 μm) and drug levels determined by HPLC.

Appendix 3

The Effect of Quaternary Ammonium Palmitoyl Glycol Chitosan Molecular Weight on the Encapsulation of Propofol

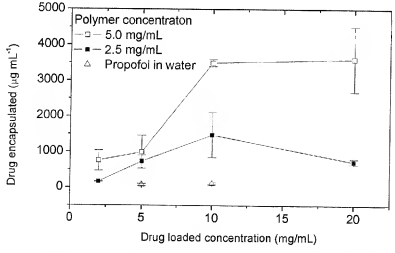

Figure 2: The encapsulation of propofol by High molecular weight GCPQ E5 aggregates (Qu et al, Biomacromolecules, 2006, 7: 3452). High molecular weight GCPQE5 was probe sonicated with propofol, the resulting formulation filtered (0.45 μm) and the level of propofol encapsulated determined by HPLC. Low molecular weight GCPQE5: backbone Mw = 9.3 kDa, backbone Mn = 4.1kDa.

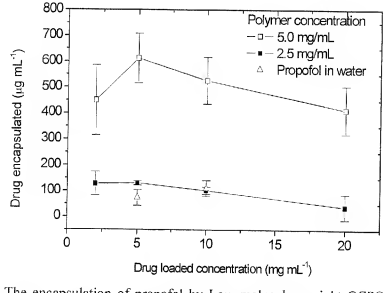

Figure 3: The encapsulation of propofol by Low molecular weight GCPQ E5 aggregates (Qu et al, Biomacromolecules, 2006, 7: 3452). Low molecular weight GCPQE5 was probe sonicated with propofol, the resulting formulation filtered (0.45 μm) and the level of propofol encapsulated determined by HPLC. Low molecular weight GCPQE5: backbone Mw = 3.6 kDa, backbone Mn = 1.9kDa.

Appendix 4

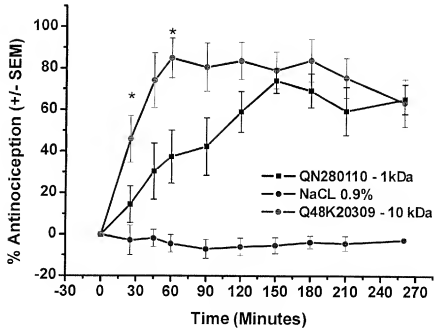

Figure 4: Mice were dosed with palmitoyl leucine enkephalin in quaternary ammonium palmitoyl glycol chitosan formulations and the analgesic activity of the formulations measured. The analgesic activity of the formulation was measured as the time taken for mice to remove their tail from a noxious thermal stimulus (55°C). The % antinociception was calculated with respect to the time taken for control animals (not dosed with enkephalin formulations) to remove their tails from the thermal stimulus. A statistically significantly higher analgesic response is obtained with the 10kDa quaternary ammonium palmitoyl glycol chitosan when compared to the 1kDa quaternary ammonium palmitoyl glycol chitosan. * = $p < 0.0001$.

Appendix 5

Propofol (5 mg) was dispersed into formulations containing quaternary ammonium palmitoyl glycol chitosan polymers of various molecular weight. Propofol levels were then measured by HPLC (Biomacromolecules, 2006, 7: 3452). Significantly higher levels of propofol were recovered in the 3 – 18 kDa polymers compared to the 1 kDa polymer.

Polymer Batch	**Polymer Molecular Weight (Mw, kDa)**	**Polymer Molecular Weight (Mn, kDa)**	**Polydispersity (Mw/Mn)**	**Molecular Weight Measurement Method**	**Drug Level (mg mL-1)**
QN280110	Not applicable	1.0	Not applicable	Mass spectrometry	0.144 ± 0.008*
Q48R2421010	Not applicable	3.5	Not applicable	MALDI-TOF	0.694 ± 0.129
Q48K20309	11.4	9.9	1.16	GPC-MALLS	0.703 ± 0.210
Q15210110	17.9	16.1	1.11	GPC-MALLS	0.687 ± 0.015

* $p < 0.05$ (significantly different from other polymer samples)

Appendix 6

The dynamic viscosity of various quaternary ammonium palmitoyl glycol chitosan polymer solutions was measured. The 40kDa – 174kDa polymer solutions are significantly more viscous than the 3kDa – 18kDa polymers.

Polymer Batch Number	**Polymer Molecular Weight (Mw, kDa)**	**Polymer Molecular Weight (Mn, kDa)**	**Polydispersity (Mw/Mn)**	**Method of Molecular Weight Measurement**	**Dynamic Viscosity mPa. s (Concentration = 6.75 mg mL^{-1})**	**Dynamic Viscosity mPa. s (Concentration = 20 mg mL^{-1})**
Q48R2421010	Not applicable	3.5		MALDI-TOF	0.95 ± 0.002	1.20 ±0.002
Q48K20309	11.4	9.9	1.16	GPC-MALLS	1.02 ± 0.001	1.41 ± 0.001
Q15210110	17.9	16.1	1.11	GPC-MALLS	1.13 ± 0.003	1.78 ± 0.002
Q3010210	58.8	40.3	1.48	GPC-MALLS	8.17 ± 0.03*	Outside instrument range > 70
Q2270709	75.4	50.0	1.50	GPC-MALLS	4.05 ± 0.07*	Outside instrument range > 70
QU170110	174	113.5	1.51	GPC-MALLS	7.14 ± 0.13*	Outside instrument range > 70

* $p < 0.0001$ (significantly different from low molecular weight batches)